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CENTRAL LOCATION

FACSIMILE COVER SHEET

Examiner: P. Nolan **Group:** 1644

Date: December 20, 2004

Client Code: 0148

Facsimile No.: 703-872-9306

From: Alice O. Carroll

Subject: **Paper:** **Declaration of Don E. Griswold, Ph.D. under 37 C.F.R. §1.132**
Docket No.: 0148.1135-010
Applicant: George Treacy
Serial No.: 09/942,075
Filing Date: August 28, 2001

Number of pages including this cover sheet: 38

Please confirm receipt of facsimile: Yes ___ No ___

Comments:

@PFDesktop\.ODMA/MHODMA/HBSR05;iManage,520833;1

2. I received my Ph.D. degree in Pharmacology from the University of Kansas Medical Center, Kansas City, Kansas in 1969. A copy of my curriculum vitae, which describes my educational and professional experience, is attached as Exhibit A.

3. I have published extensively in refereed publications, most of which have been focused in the areas of inflammation, immunopharmacology, and pulmonary and cutaneous pharmacology. A list of publications authored or co-authored by me is included as part of my curriculum vitae.

4. I have read the Office Action dated May 18, 2004, the Office Action dated August 21, 2003, and the art cited by the Examiner in the Office Actions, in particular the cited references of Konno *et al.* (*Int. Arch. Allergy Immunol*, 105:308-316 (1994)), Shah *et al.* (*Clin. Exper. Allergy*, 25:1038-1044 (1995)), and Lukacs *et al.* (*J. Immunol*, 154:5411-5417 (1995)). I have also read the patent application and the presently pending claims that were rejected in the Office Action.

5. Konno *et al.* examined the influence of roxithromycin (RXM), a macrolide antibiotic, and polyclonal rabbit anti-mouse TNFα antibodies on cytokine appearance in mouse lung extract induced by lipopolysaccharide (LPS) inhalation and on bronchial responsiveness (BR) to methacholine (Mch) in LPS-treated mice. Although inhalation of LPS causes pulmonary inflammatory responses and an increase in BR, it is not considered as an animal model for asthma. Thus, results obtained using the LPS mouse model would not provide evidence for the treatment of asthma.

6. Shah *et al.* summarize the scientific rationale available in 1995 that supported TNFα as an attractive target for asthma. In particular, Shah *et al.* report results showing (1) increased levels of TNFα in sputum of patients with acute attacks of asthma; (2) increased number of cells expressing TNFα mRNA in bronchoalveolar lavage (BAL) fluid of stable atopic asthmatic subjects when compared to BAL of normal subjects; and (3) TNFα levels up

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AOC/HL
December 3, 2004

PATENT APPLICATION
Attorney's Docket No : 0148 1135-010

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	George Treacy		
Application No.:	09/942,075	Group Art Unit:	1644
Filed:	August 28, 2001	Examiner:	Nolan, P.
Confirmation No.:	6161		

For: ANTI-TNFα ANTIBODIES IN THERAPY OF ASTHMA

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Commissioner for Patents, P.O Box 1450 Alexandria, VA 22313-1450, or is being facsimile transmitted to the United States Patent and Trademark Office on.

12/20/04 Linda Woodhouse
Date Signature

LINDA WOODHOUSE
Typed or printed name of person signing certificate

DECLARATION OF DON E. GRISWOLD, PH.D.
UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Don E. Griswold, Ph.D., declare and state that:

1. I have been employed at Centocor, Inc., 200 Great Valley Parkway, Malvern, PA 19355 since 2001, most recently as Senior Director and Head, Department of Immunobiology. I have been advised that Centocor is the assignee of the entire right, title and interest of the subject application.

2. I received my Ph.D. degree in Pharmacology from the University of Kansas Medical Center, Kansas City, Kansas in 1969. A copy of my curriculum vitae, which describes my educational and professional experience, is attached as Exhibit A.

3. I have published extensively in refereed publications, most of which have been focused in the areas of inflammation, immunopharmacology, and pulmonary and cutaneous pharmacology. A list of publications authored or co-authored by me is included as part of my curriculum vitae.

4. I have read the Office Action dated May 18, 2004, the Office Action dated August 21, 2003, and the art cited by the Examiner in the Office Actions, in particular the cited references of Konno *et al.* (*Int. Arch. Allergy Immunol.*, 105:308-316 (1994)), Shah *et al.* (*Clin. Exper. Allergy*, 25:1038-1044 (1995)), and Lukacs *et al.* (*J. Immunol.*, 154:5411-5417 (1995)). I have also read the patent application and the presently pending claims that were rejected in the Office Action.

5. Konno *et al.* examined the influence of roxithromycin (RXM), a macrolide antibiotic, and polyclonal rabbit anti-mouse TNFα antibodies on cytokine appearance in mouse lung extract induced by lipopolysaccharide (LPS) inhalation and on bronchial responsiveness (BR) to methacholine (Mch) in LPS-treated mice. Although inhalation of LPS causes pulmonary inflammatory responses and an increase in BR, it is not considered as an animal model for asthma. Thus, results obtained using the LPS mouse model would not provide evidence for the treatment of asthma.

6. Shah *et al.* summarize the scientific rationale available in 1995 that supported TNFα as an attractive target for asthma. In particular, Shah *et al.* report results showing (1) increased levels of TNFα in sputum of patients with acute attacks of asthma; (2) increased number of cells expressing TNFα mRNA in bronchoalveolar lavage (BAL) fluid of stable atopic asthmatic subjects when compared to BAL of normal subjects; and (3) TNFα levels up

to 20 times greater in BAL fluid of patients with symptomatic asthma than asymptomatic patients. From these results, Shah *et al.* concluded that "it appears that there is a disease related upregulation of TNFα which suggests that this cytokine plays a key role in ongoing airways inflammation" (page 1040, column 2, lines 6-8).

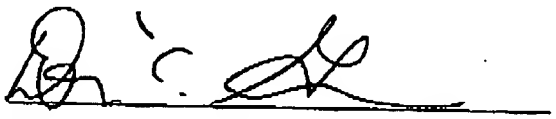
Shah *et al.* also report results indicating that TNFα may be associated with acquired airway hyperresponsiveness, a pathophysiological hallmark of asthma, and provided the scientific rationale available in 1995 that supported TNFα as an attractive target for asthma. However, Shah *et al.* do not disclose scientific data showing that blocking TNFα would treat asthma. Accordingly, Shah *et al.* do not provide evidence that would have taught one of ordinary skill in the art to effectively treat asthma or airway inflammation associated with in a human patient with an anti-TNFα antibody.

7. Lukacs *et al.* examined the role of TNF in the initiation and maintenance of leukocyte recruitment in airway inflammation induced by intratracheal challenge with soluble parasite (*Schistosoma mansoni*) egg Ag (SEA). The SEA-induced airway inflammation model used by Lukacs *et al.* is a model of Th2 cell-induced eosinophilic airway inflammation that allows for the study of the recruitment of various leukocyte subsets to lungs and airways. This model of airway inflammation has both an early neutrophilic (8-h) and a later (48-h) eosinophilic airway infiltration.

However, Lukacs *et al.* treated SEA-challenged mice with a TNF receptor antagonist (sTNFR-Fc), not with an anti-TNFα antibody. Since more than one cytokine can bind to TNFR, sTNFR-Fc is not as specific as a neutralizing anti-TNFα mAB. As a matter of fact, TNF receptor antagonists antagonize the activities of both TNFα and TNFβ (lymphotoxin), whereas anti-TNFα antibodies do not neutralize the activity or effect of lymphotoxin.

Thus, Lukacs *et al.* do not provide data that would have led one of ordinary skill in the art to conclude that administration of an anti-TNF antibody to a subject would be effective in methods of treating asthma, in methods of treating airway inflammation associated with asthma, and in methods of reducing accumulation in lungs of inflammatory cells associated with asthma.

8. I declare that all statements made in this Declaration of my own knowledge are true and that all statements made on information and belief are believed to be true. Moreover, these statements are made with the knowledge that willful false statements and the like made by me are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.



Don E. Griswold, Ph.D.

Dec. 16, 2004

Date

Attachment

Exhibit A Curriculum vitae, including list of publications

CURRICULUM VITAE

Don E. Griswold, Ph.D.

November, 2004

ADDRESS: Centocor, Inc.
Department of Immunobiology
200 Great Valley Parkway
Malvern, PA USA 19355-1307

TELEPHONE: (610) 651-6994
FAX: (610) 240-4064

DATE AND PLACE OF BIRTH: June 24, 1943, Newton, Kansas

EDUCATION:

Institution	Degree	Date Received	Major(s)
University of Kansas Medical Center Kansas City, Kansas	Ph.D.	1969	Pharmacology
Emporia State University Emporia, Kansas	B.A.	1965	Microbiology and Chemistry

EXHIBIT
A

PROFESSIONAL EXPERIENCE:

CENTOCOR, INC.

Senior Director and Head, Department of Immunobiology (January 2001-Present)
I am currently directing efforts to discover and promote biological therapeutics with potential utility in the treatment of immune-mediated inflammatory disorders. In addition, support of collaborations among Centocor Research departments as well as J&J member companies involved in this area of research is on going.

SMITHKLINE BEECHAM PHARMACEUTICALS

Director, Department of Pulmonary Pharmacology (June 1998-December 2000)
I conducted and directed broad-based research in the areas of pulmonary and cutaneous pharmacology. My efforts involved the molecular biological and biochemical evaluation of mediators in different disease models. In addition, we developed *in vivo* models with the key feature of providing evidence of mechanism of action and proof of concept. This research was directed toward several disease targets including asthma, COPD, psoriasis, atopic dermatitis and eczema.

Associate Director, Department of Immunopharmacology (1994-1998)
I conducted and directed broad-based research in inflammation and immunopharmacology. My effort involved the search for inflammation-associated novel gene expression in different disease models and identification of human homologs. In addition, we developed both *in vitro* and *in vivo* models with the key feature of providing evidence of mechanism of action.

Assistant Director, Department of Inflammation and Respiratory Pharmacology. (1990-1994)
I coordinated inflammation research efforts and provided critical in vivo and/or in vitro model systems for several major strategic areas. We identified and brought forward development candidates in several of these areas.

Assistant Director, Department of Immunology. (1986-1990)
Initially as Deputy Director of the Inflammation and Arthritis Program, and later supervising that position, I coordinated a team of thirty scientists in the discovery and development of antiinflammatory and antiarthritic drugs. A unique class of antiinflammatory/antiarthritic agents (pyrroloimidazoles) was discovered and the lead compound was recommended for clinical development. Several compounds were identified for pre-development consideration. In addition, selective 5-LO agents were discovered and promoted as anti-asthmatic agents.

Senior Investigator, Department of Immunology. (1978-1986)
I supervised several associates and one Ph.D. and his staff in conducting in vitro and in vivo/ex vivo assays to measure the inhibition of leukotriene and prostanoid production. In addition, key model systems to differentiate lipoxygenase inhibitors from cyclooxygenase inhibitors were developed and adopted. Key findings were the immunoregulatory actions of Ridaura (auranofin), the action of histamine type-2 receptor antagonists on T suppressor cell function, and the characterization of the immunosuppressive effects of concanavalin A.

November, 2004

Associate Senior Investigator, Department of Pharmacology. (1974-1978)
I conducted adjuvant rat studies as a primary in vivo screen for antiarthritic agents. I also participated in the development of auranofin (Ridaura) and developed immunological models to explore the immunopharmacology of key compounds of interest. I had responsibility for the majority of the pharmacology conducted in the Arthritis and Immunoregulatory Research Mission.

BROWN UNIVERSITY
Division of Bio-Medical Sciences and Department of Medicine
Roger Williams General Hospital
Providence, RI

Assistant Professor (Research) of Medicine. (1973-1974)
I participated in fundamental cancer research. Our findings included demonstration of selective immunosuppression by cytostatic/cytotoxic drugs. I acted as advisor to 3 Masters of Medical Science students, lectured and conducted laboratory experiences for Brown University students.

University Instructor. (1971-1973)
I conducted research in cancer and immunopharmacology. I participated in teaching of Brown University students.

Research Fellow. (1969-1971)
I evaluated and developed methods to examine drug hypersensitivity and initiated work on immunoregulatory action of cytotoxic agents.

UNIVERSITY OF KANSAS MEDICAL CENTER
Department of Pharmacology
Rainbow Boulevard
Kansas City, Kansas

Graduate Student Laboratory Assistant. (1966-1969)
I was responsible for setup and conduct of the Pharmacology laboratory experience for medical students. I was also responsible for pharmacology lectures for nursing students.

EMPORIA STATE UNIVERSITY
Department of Microbiology
Emporia, Kansas

Research Assistant. (1963-1965)
I conducted research in microbiology and immunology and initiated research on assays of antibody-forming cells in amphibia (Rana pipiens). The work was presented at a regional meeting of the American Society for Microbiology.

HONORS, AWARDS, AND MEMBERSHIPS:

- Who's Who in Frontier Science and Technology Nomination Committee, Alfred P. Sloan Jr. Prize, General Motors Cancer Research Foundation
- Lambda Delta Lambda
- Sigma Xi
- American Association for Cancer Research
- American Association for the Advancement of Science
- New York Academy of Science
- American Society for Pharmacology and Experimental Therapeutics
- The Society for Investigative Dermatology
- American Thoracic Society
- Centocor Research Executive Committee Member
- J&J Immunologically-Mediated Inflammatory Disorders/Pulmonary Therapeutic Area Optimization Committee (TAOC) and Core TAOC Member

EDITORIAL RESPONSIBILITIES:

Inflammation Research
Cancer Research
Science
International Journal of Immunopharmacology
Expert Opinion on Therapeutic Patents
British Journal of Pharmacology
Journal of Pharmacology and Experimental Therapeutics
General Pharmacology, The Vascular System
American Journal of Respiratory and Critical Care Medicine

CONFERENCES AND SYMPOSIA ORGANIZED:

Workshop on Inflammation Models IRA 1994

INVITED PRESENTATIONS, SEMINARS AND SYMPOSIA:

Griswold. D.E. Pharmacology of Cytokine Suppressive Anti-Inflammatory Drugs / CSAID. Presented at SRI Conference entitled "On the Cutting Edge of Anti-Inflammatory Drug Discovery" New York, New York March 13-14, 1995.

Griswold, D.E. Pharmacology of an Emerging Dermatology Portfolio. Presented at Galderma, Paris, France, October 16, 1996.

Griswold, D.E. Pharmacology of an Emerging Dermatology Portfolio. Presented at LEO Pharmaceuticals, Copenhagen, Denmark, October 18, 1996.

Griswold, D.E. Pharmacology of an Emerging Dermatology Portfolio. Presented at Schering AG, Berlin, Germany, November 1, 1996.

Griswold, D.E. Pharmacology of CSBP/p38 Inhibitors. Presented to Department of Dermatology, University of Nijmegen, Nijmegen, The Netherlands. February 6, 1997.

Griswold, D.E. Pharmacology of MAP Kinase Inhibitors. Presented at IBC Conference entitled " New Drugs for Asthma." National Heart and Lung Institute, London, UK June 16 and 17, 1998.

Griswold, D.E. Pharmacology of p38 Kinase Inhibitors. Presented at an Imperial College Conference entitled "Conquering Airway Inflammation in the 21st Century", National Heart and Lung Institute London, UK September 14-16, 1998.

Griswold, D.E. Invited Lecture on Eiscosanoid Pharmacology. Thomas Jefferson University. Oct 1, 1998.

Griswold, D.E. Institut Pasteur EuroConference on Chronic Lung diseases, talk entitled "Will antibodies have a role in the therapy of COPD?" Paris, France June 27-29, 2001

Griswold, D.E. Invited presentation to Groningen Research Institute for Asthma and COPD. Groningen, The Netherlands January, 2003

Griswold, D.E. Invited presentation to Professor Stephen Holgate and staff at University of Southampton, UK, July, 2003

Griswold, D.E. and Anuk Das. Invited presentation to Professor Peter Barnes and Trevor Hansel at National Heart and Lung Institute, London, UK, April, 2004

PATENTS:

1. U.S. Patent 4,686,231 issued August 11, 1987.
2. U.S. Patent 4,778,806 issued October 18, 1988.
3. U.S. Patent 4,780,470 issued October 25, 1988.
4. U.S. Patent 4,794,114 issued December 27, 1988.
5. U.S. Patent 5,134,150 issued July 28, 1992.
6. U.S. Patent 5,317,019 issued May 31, 1994.
7. U.S. Patent 5,824,696 issued October 20, 1998.
8. U.S. Patent 5,929,096 issued July 27, 1999.
9. U.S. Patent 5,981,538 issued November 9, 1999

PATENTS (continued)

10. U.S. Patent 6,759,410 issued July 6, 2004

PUBLICATIONS :

1. Griswold, D.E., and Uyeki, E.M.: Immunosuppressant effect of salicylates and quinine on antibody-forming cells. Eur. J. Pharmacol. 6:56-60 (1969).

2. Griswold, D.E., and Uyeki, E.M.: The effect of 5-fluorouracil on direct and developed spleen hemolysin plaque-forming cells in mice. Tumori 12:109-114 (1969).

3. Griswold, D.E., and Uyeki, E.M.: Quantitation of immediate hypersensitivity in various mouse strains. Int. Arch. Allergy and Ap. Immun. 40:682-690 (1971).

4. Griswold, D.E., Heppner, G.H., and Calabresi, P.: Selective suppression of humoral and cellular immunity with cytosine arabinoside. Cancer Res. 32:298-301 (1972).

5. Calabresi, P., Griswold, D.E., Poplin, E.A. and Heppner, G.H.: Selective immunosuppression by drugs in complex immune responses. Pharmacology and the future of man. Proc. 5th Intl. Cong. Pharmacol. 5:421-430 (1972).

6. Griswold, D.E., Heppner, G.H., and Calabresi, P.: Alteration of immunocompetence by mammary tumor virus. J. Natl. Cancer Inst. 50:1035-1038 (1973).

7. Laing, C.A., Griswold, D.E., and Heppner, G.H.: A new method for the quantitation of tumor growth in situ: Measurement by plethysmography. J. Natl. Cancer Inst. 51:1345-1348 (1973).

8. Mourachian, H., and Griswold, D.E.: A method for permanently recording micro-hemagglutination patterns. J. Immunol. Meth. 4:29 (1974).

9. Griswold, D.E., DiLorenzo, J.A., and Calabresi, P.: Quantitation and pharmacological dissection of oxazolone-induced contact sensitivity in the mouse. Cellular Immunol. 11:198-204 (1974).
10. Griswold, D.E., and Calabresi, P.: Human leukocyte reactivity to penicilloylated erythrocytes. Blood 44:501-509 (1974).

11. DiLorenzo, J.A., Griswold, D.E., Bareham, C.R., and Calabresi, P.: Selective alteration of immunocompetence with methotrexate and 5-fluorouracil. Cancer Res. 34:124-128 (1974).

12. Bareham, C.R., Griswold, D.E., and Calabresi, P: Synergism of methotrexate with Imuran and with 5-fluorouracil and their effects on hemolysin plaque-forming cell production in the mouse. Cancer Res. 34:571-575 (1974).

13. Medina, D., Stockman, G., and Griswold, D.E.: Significance of chemical carcinogen-induced immunosuppression in mammary tumorogenesis in Balb/c mice. Cancer Res. 34:2663-2668 (1974).

14. Heppner, G.H., Griswold, D.E., DiLorenzo, J.A. Poplin, E.A., and Calabresi, P: Selective Immunosuppression by Drugs in Balanced Immune Responses. Fed. Proc. 33:1882-1885 (1974).

15. Griswold, D.E., Heppner, G.H., and Calabresi, P.: Stimulation of hemolysin plaque-forming cells by iododeoxyuridine. Cancer Res. 35:88-93 (1975).

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17. Griswold, D.E. and Walz, D.T. : Condition-dependent immunoregulatory control of contact sensitivity by levamisole. Inflammation 2:277-284 (1977).

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19. Walz, D.T., and Griswold, D.E.: Immunopharmacology of gold sodium thiomalate and auranofin (SK&F D-39162): Effects on cell-mediated immunity. Inflammation 3:117-128 (1978).

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21. Walz, D.T., DiMartino, M.J., Griswold, D.E.: Immunopharmacology of auranofin and gold sodium thiomalate: Effects on humoral immunity. J. Rheumatology 6:74-81 (1979).

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23. Walz, D.T., Griswold, D.E., DiMartino, M.J., and Bumbier, E.E.: Effect of auranofin dose regimen change upon cell-associated gold in rheumatoid arthritis patients. J. Rheumatology 8:829-832 (1981).

24. Griswold, D.E., and Walz, D.T.: The effect of selected immunoregulatory agents on low grade contact sensitivity. Inflammation 6:55-62 (1982).

25. Badger, A.M., Griswold, D.E., and Walz, D.T.: Augmentation of Concanavalin A-induced immunosuppression by indomethacin. Immunopharmacology 4:149-162 (1982).

26. Walz, D.T., DiMartino, M.J., and Griswold, D.E.: Mechanisms of action of auranofin: Effects on humoral immune response. J. Rheumatol. 9:32-36 (1982).

27. Walz, D.T., DiMartino, M.J., and Griswold, D.E.: Comparative pharmacology and biological effects of different gold compounds. J. Rheumatol. 9:54-60 (1982).

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32. Walz, D.T., Griswold, D.E., DiMartino, M.J., and Bumbier, E.E.: Patterns of decay of serum, blood, and cell-associated gold following intravenous administration of auranofin, gold sodium thiomalate and aurothioglucose to rats. J. Rheumatology 10:117-120 (1983).

33. Hanna, N., DiMartino, M.J., Griswold, D.E., and Poste, G.: Immunology of auranofin- An overview. Excerpta Medica, Current Clinical Pratice Series, No. 7, pp. 60-70 (1983).

34. Walz, D.T., DiMartino, M.J., and Griswold, D.E.: Differences in the mechanism of action between oral and parenteral gold. Rheumatology. 8:99-117 (1983).

35. Griswold, D.E., Badger, A.M., Bender, P.E., Sitrin, R.D., Antell, L., Greig, R.G., and Poste, G.: Differential effects of intact subunits and nicked fragments of concanavalin A on immune functions in vitro. J. Immunol. 131:1626-1628 (1983).

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44. Griswold, D.E., Antell, L., Bender, P.E., Hanna, N., and Poste, G.: Induction of suppressor cells, interleukin-2 production, and mitogenesis with monomeric concanavalin A: Different action of tetrameric and monomeric concanavalin A. Molecular Immunol. 22:1311-1316 (1985).

45. Griswold, D.E., Webb, E.F., Clark, M.A., and Mong, S.: Phlogistic activity of leukotriene D_4 in the mouse. Inflammation 10:1-7 (1986).

46. Griswold, D.E., Hillegass, L., Antell, L., Shatzman, A., and Hanna, N.: Quantitative western blot assay for measurement of the murine acute phase reactant, serum amyloid P component. J. Immunol. Methods. 91:163-168 (1986).

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